Transverse Relaxometry for Brain Iron: Comparison of Seven Approaches

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Introduction: Iron accumulation in subcortical gray matter (GM) has been increasingly studied and described in neurodegenerative and inflammatory diseases including multiple sclerosis (MS) [1]. A range of transverse relaxation rates (R_2, R_2^* and R_2') may be measured to provide information about subtle iron-related changes, each with varying advantages. At high magnetic fields, the spin-echo based R_2 is more difficult to measure due to radio frequency (RF) non-uniformity and RF heating concerns, while the gradient echo R_2^* may suffer from increased background field gradients, for example near air-tissue interfaces. With appropriate corrections, both R_2 (stimulated echo compensation) and R_2^* (background gradient removal) can be performed effectively and enable the determination of the difference R_2', which may be more specific to iron accumulation. At the standard field strength of 1.5 T, both measures are more easily performed, but iron specificity may be more limited. The use of both low and high field strength also enables field strength difference measures known as field dependent R_2 increase (FDRI). In this work, quantitative R_2 and R_2^* maps were obtained with 2D multiecho spin echo sequence in multislice mode using stimulated echo compensation [2] and 3D multi-echo gradient echo susceptibility compensation [3] in presence of heterogeneous RF and B_0 fields respectively. The purpose of the study is to compare the iron sensitivity of R_2, R_2^*, R_2' and FDRI mapping methods in subcortical gray matter using 1.5 T and 4.7 T.

Methods: Nine healthy subjects (36±10 years, age range 25-59, 5 male, 4 female) were scanned using 4.7 T and 1.5 T MRI systems. All subjects provided informed consent according to the institutional protocols. R_2 maps were acquired using stimulated echo compensation [2] from 2D multi-echo spin echo images with 4000 ms TR, 10 ms ESP, 5 ETL, 4 mm slice thickness, 8 slices, 8 mm slice gap and 256 x 145 imaging matrix, keeping the parameters consistent for both field strengths. Multi-echo 3D GRE imaging was performed at both field strengths to obtain R_2^* maps. At 4.7 T ten echoes were recorded without flow compensation (TE1 of 2.93 ms, 4.1 ms ESP) with 44 ms TR, flip angle of 10°, 50 kHz BW, 4 mm slice thickness, 256x192x40 imaging matrix, scan time 9.39 min. While at 1.5 T scan parameters were: 6 ms TE1, 7 ms ESP, 5 ETL, 44 ms TR, 10° flip angle, 152 Hz/pixel BW, in plane resolution 1x1 mm^2 and scan time 22.75 min. Average R_2, R_2^* values were measured in frontal white matter, cortical gray matter, globus pallidus, caudate nucleus, putamen, substantia nigra and red nucleus. Regressions of R_2, R_2^*, R_2' and FDRI versus non-heme iron were calculated using ages and the equations given in [4]. FDRI and R_2' are obtained as $FDRI = R_2^{4.7T} - R_2^{1.5T}$ and $R_2' = R_2^* - R_2$ on the same subject.

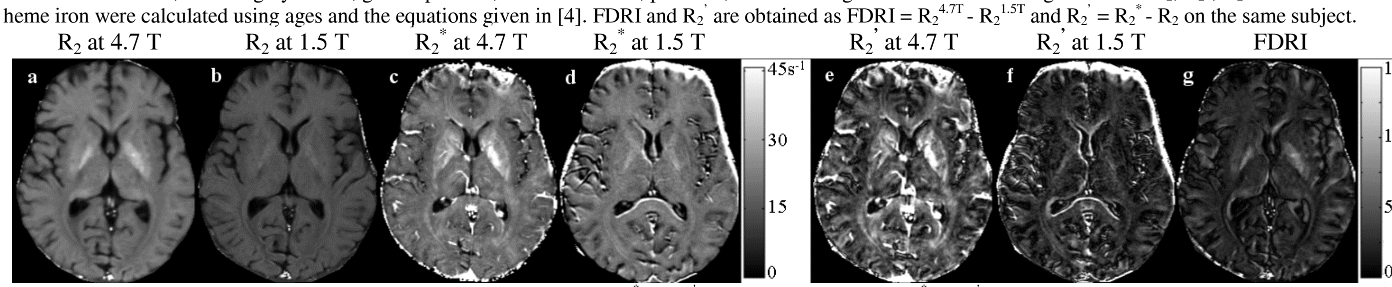

Figure 1: In-vivo maps: a) R_2, c) R_2^*, e) R_2' at 4.7 T while b) R_2, d) R_2^*, f) R_2' at 1.5 T; g) FDRI.

Results: Fig. 1 compares R_2, R_2^*, R_2' and multi-slice FDRI maps from one volunteer obtained at 1.5 T and 4.7 T. Iron rich deep gray matter has high conspicuity at 4.7 T and in the FDRI map. Average relaxation rates at both field strengths are shown in Table 1. Very high relaxation rates are observed in globus pallidus and substantia nigra. A range of transverse relaxation rates (R_2, R_2^* and R_2') from eight brain regions at 4.7 T, R_2 at 1.5 T and the difference between R_2 values at both field strengths (FDRI) are plotted against regional non-heme iron [Fe] as shown in Fig. 2. Linear regression analysis (Table 2) of relaxation rates R_2, R_2^*, R_2' at 4.7 T and FDRI versus non-heme iron provides strong correlations (R^2 = 0.88 R_2^*, 0.84 R_2', 0.80 R_2 at 4.7 T and 0.82 FDRI at the $p < 0.05$ significance level) with slopes 0.61, 1.95, 1.46 and 0.46 in [s^{-1}/mg Fe per 100 g wt. tissue] and intercepts 13.89, 17.37, 3.19 and 2.62 in [s^{-1}] respectively. Regression slopes for all transverse relaxation rates (R_2, R_2^*, R_2') were around 3 to 4 times greater at 4.7 T than 1.5 T indicating the linear field dependence from ferritin-based relaxation [5]. Although R_2^* provides highest correlation with iron, R_2' and FDRI maintain a linear relationship with iron, yet have small intercepts.

Discussion: We have demonstrated a strong correlation between estimates on non-heme iron concentrations in deep gray matter and transverse relaxation rates as well as FDRI when using stimulated echo compensation for R_2 and 3D multi gradient echo with linear background gradients correction for R_2^*. Results for multi-slice R_2 are consistent with previous work where imaging was performed only in single slice mode using twice refocusing adiabatic pulses [5]. Considering only caudate, putamen and globus pallidus we obtained better results (R^2 = 0.93 R_2^*, 0.88 R_2', 0.85 R_2 at 4.7 T) compared to the recent work at 3.0 T [6]. However, R_2^* and R_2' are more sensitive to macroscopic field inhomogeneities created by ferritin in the brain. Small intercept of R_2' versus iron indicates a specific sensitivity to iron in deep gray matter structures. Iron sensitivity measurement in white matter territories is challenging when using R_2^* or R_2' due to their dependency on fiber orientation as well as the presence of macromolecular fraction [6]. FDRI allows to assess true iron content in white matter and subtracted out this macromolecular fraction confound as shown in Fig. 2 where all transverse relaxation rates for frontal white matter lie above the regression line except for FDRI.

Conclusion: Increased iron sensitivity can be achieved with quantitative assessment of transverse relaxation rates R_2, R_2^* and R_2' at 4.7 T as well as using FDRI at 4.7 T combined with 1.5 T. R_2^* performs best for iron measurement as R_2^* is the sum of relaxation rates R_2 and R_2' that accumulate irreversible and reversible iron effects. Whereas R_2' provides more specific sensitivity to iron as suggested by small intercept. FDRI also provides specific brain iron measure by correcting macromolecular fraction confounds but required two field strengths.

References: [1] Schenck JF, Zimmerman EA, NMR Biomed 17(7) 2004. [2] Lebel RM, Wilman AH, MRM 64(4) 2010. [3] Lebel RM, Wilman AH, ISMRM-ESMRMB (p. 5002) 2010. [4] Hallgren B et al. J Neurochem, 3(1) 1958. [5] Mitsumori et al. MRM 68(3) 2012. [6] Sedlacik J et al. NeuroImage 2013.

Table 1: Transverse relaxation rates R_2, R_2^* and R_2' (s^{-1}) at 1.5 T and 4.7 T

	Frontal white matter		Caudate nucleus		Putamen		Globus Pallidus		Substantia nigra	
	4.7 T	1.5 T	4.7 T	1.5 T	4.7 T	1.5 T	4.7 T	1.5 T	4.7 T	1.5 T
R_2	18.6±0.8	13.5±0.8	17.4±1.0	11.6±0.3	19.1±0.8	12.5±0.4	27.4±3.8	14.7±1.4	26.5±1.0	14.4±0.7
R_2^*	31.6±1.6	18.0±0.5	29.3±2.3	15.8±0.8	34.8±2.7	18.0±1.2	58.3±2.2	25.1±3.4	59.2±4.4	26.4±3.8
R_2'	13.7±1.6	4.9±0.6	12.6±2.4	4.2±0.7	15.5±3.1	5.7±1.1	33.2±3.0	10.9±4.6	34.9±4.6	11.6±3.7

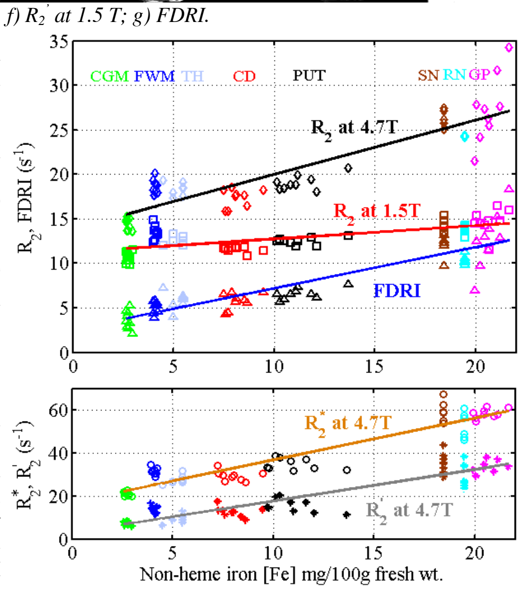

Figure 2: Scatter plots of transverse relaxation rates (R_2, R_2^* and R_2') and FDRI versus estimates of non-heme iron concentrations. Solid lines were obtained using linear regression analyses. Cortical gray matter (CGM), frontal white matter (FWM), globus pallidus (GP), caudate nucleus (CD), putamen (PUT),substantia nigra (SN),red nucleus (RN) and Thalamus (TH).

Table 2: Coefficients of slopes(s^{-1}/mg Fe/100 g wt.) and intercepts(s^{-1}) at 1.5 T and 4.7 T

Comparison	B_0	Slope	Intercept	R^2
R_2 vs.[Fe]	4.7	0.61±0.04	13.89±0.49	0.80
	1.5	0.15±0.02	11.27±0.25	0.47
R_2^* vs. Fe]	4.7	1.95±0.09	17.37±1.12	0.88
	1.5	0.63±0.04	12.61±0.59	0.74
R_2' vs. [Fe]	4.7	1.46±0.08	3.19±0.99	0.84
	1.5	0.47±0.04	1.46±0.54	0.65
FDRI vs. [Fe]		0.46±0.03	2.62±0.36	0.82